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LETTERS AND CORRESPONDENCE

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Implications of Prominent Cytologic Dysplasia Persisting in the Marrow of a Patient With CML Even After the Spontaneous Disappearance of the Philadelphia Chromosome

To the Editor: Only one reported patient with chronic myeloid leukemia (CML) entered a complete clinical and cytogenetic remission without previous chemotherapy [1]. There are a few reports of patients with CML who achieved a "spontaneous" cytogenetic remission but all these patients were initially treated with busulfan/hydroxyurea [2–4]. In three instances Bcr analysis on such patient's DNA was also negative for Bcr rearrangement. We discuss implications of prominent cytologic dysplasia persisting in the marrow of a patient with CML, even after spontaneous disappearance of the Philadelphia chromosome (Ph).

A 73-year-old male farmer presented in June 1992 with malaise. Physical examination was unremarkable. Hb was 10.4 g/dl, white blood cell (WBC) count 22×10^9/L, and platelet count 173×10^9/L. Blood film and bone marrow appearance were consistent with chronic-phase CML. Dysplastic features characteristic of chronic myeloproliferative disorders (e.g., pseudo-Pelger-Huët anomaly, micromegakaryocytes, hypogranulated neutrophils, giant metamyelocytes) were conspicuously present in the marrow. The karyotype demonstrated Ph mosaicism with a classical translocation in 10/40 unstimulated marrow metaphases. Without any cytotoxic therapy attempted, the patient developed pancytopenia over a period of only 10 days. His Hb was 7.6 g/L, WBC count 3.7×10^9/L, and platelets 130×10^9/L. The peripheral blood film became normal. Repeated cytogenetic examination on the marrow showed normal karoytype in 50/50 unstimulated metaphases. The rearranged M-bcr was entirely negative by Southern blot assay (PCR analysis was not done). However, pelgeroid neutrophils, micromegakaryocytes, and normal-size megakaryocytes (but with distinctly dysplastic nuclei) could still be seen.

In November 1992, the WBC count rose to 100.0×10^9/L. Blood film was again characteristic of chronic phase CML with the reappearance of Ph in 93% (1/14) of unstimulated metaphases. An integral dose of 72 mg of busulfan was given over 9 consecutive days. Leukopenia of 2.7×10^9/L developed with normal formula. Coincidentally, Hb fell to 8.7 g/dl and platelets to 67×10^9/L. Busulfan-induced marrow hypoplasia was demonstrated by trephination. Dysplastic marrow features persisted despite the fact that the karyotype was again normal in 50/50 unstimulated metaphases (marrow). Repeat extensive analysis of surveillance marrow (January and April, 1993) showed continued Ph negativity, with prominent dysplastic features still persisting. The patient received three doses (about 900 ml) of separated erythrocytes to correct anemia on three occasions. The persistence of morphologic dysplasia in the Ph negative marrow makes it unlikely that engraftment occurred.

Fourteen months since diagnosis, bimodal karyotype changes were noted in the marow: 46XY (14%), 46,XY, Ph(20%) and 45,XY der(1), der(1), 6p-, der(13), -4(66%). The myelogram showed accelerated evolution of CML (7%, Sudan-positive, blasts). Thoracic radiographic examination showed right pleural effusion. Microscopy of the effusate showed blast crisis in pleura with karyotype aberrations the same as in the marrow. Intrapleural instillation of Ara-C and systemic chemotherapy eradicated all karotype subclones split off from the "basic" 46,XY Ph-negative, but dysplasia-producing, one. The Ph-negative chronic phase was reestablished for the next 7 months. A fatal crisis (69% blasts in marrow) indolent to treatment and with a different clone evolution in the marrow [46, XY, Ph (27%), 61, XY, 2Ph, +8, +9, +10, +12, +13, +14, +17, +18, +19, +20, +21, +X, +M (73%)] appeared 21 months after the diagnosis.

The unrelenting trilineage dysplasia throughout the course of disease may lend support to previous evidence [5,6] that an introductory stage of CML may exist in some patients preceding the appearance of the Ph. The residual Ph-negative "protoclone" may have had a growth advantage over its Ph-positive subclones during exposure to busulfan. The persistance of prominent morphologic dysplasia would therefore imply not only a multistep but also a multipronged [7] program of clonal evolution in CML with survival of the initial Ph-negative clone late in the disease.

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Antiphospholipid Syndrome: A Case Demonstrating Diagnostic Challenge

To the Editor: Antiphospholipid syndrome (APS) is defined as recurrent thrombosis together with (1) moderately to highly elevated serum anticardiolipin antibodies, or (2) a prolonged phospholipid-dependent clotting test such as activated partial thromboplastin time (APTT) that does not normalize upon mixing patient with normal plasma. We report a case of recurrent thrombosis associated with an ill-defined autoimmune disease. Despite the clinical picture markedly resembling APS, standard APTT was repeatedly normal, and anticardiolipin antibodies were normal to only mildly elevated. The diagnosis was finally made on the basis of prolonged APTT, using rabbit brain phospholipid with silica instead of bovine brain phospholipid with ellagic acid, and on positive hexagonal phase phospholipid antibody neutralization test (HexPPANT).

A previously healthy white man presented with pulmonary embolism and two episodes of blue toe at age 57. Then, with coumadin, he was well until 1 year prior to death, at age 61. During the last year of life, he suffered from recurrent bouts of presumably autoimmune pancreatitis. An extensive workup for other causes of pancreatitis and for known autoimmune diseases was unyielding. The following nonspecific abnormalities were present: enlarged pancreas without pseudocysts, calcifications or dilated ducts by CT, ANA 1:320, ESR >100 mm/hr, lymphocytopenia (0.6–0.9 $\times$ 10^9/L), anemia (hemoglobin 80–130 g/dl), thrombocytopenia (90–150 $\times$ 10^9/L), hypocellular marrow (80–90% fat, 10–20% hematopoietic cells), and anergy by skin tests.

Four months prior to death, the patient stopped coumadin for 3 months. During this period, he developed two transitory ischemic attacks, adrenal insufficiency, livedo reticularis, platelet count drop to 60 $\times$ 10^9/L, and serum creatinine elevation to 3.5 mg/dl with microscopic erythrocyturia and proteinuria (3.7 g/day). Renal angiograms revealed amputation of renal artery branches, suggesting thromboembolism. CT disclosed wedge-shaped areas of renal cortical thinning, suggesting infarcts. Renal biopsy showed multiple arteriolar and capillary thrombi. Anticardiolipin IgM was normal on two determinations; anticardiolipin IgG was once 11 GPL (normal) and once 19 GPL (mildly elevated) (ELISA). Prothrombin time was normal on 5/5 determinations. APTT using bovine brain phospholipid with ellagic acid (Activated Thrombofax, Ortho, Raritan, NJ) was normal on 4/5 determinations and slightly abnormal on 1/5 determinations (patient 29, control 25 sec). APTT using rabbit brain phospholipid and silica (Auto APTT, Organon-Teknika, Durham, NC) was moderately prolonged (patient 55, control 34, 1:1 mix, 44 sec). Dilute Russell Viper venom test (Bioclot, Biopool, Burlington, Canada) was normal (50 sec, normal 31–54 sec). HexPPANT (Staclot, American Bioproducts, Parsippany, NJ) was moderately abnormal (16 sec, normal <10 sec). Antithrombin III, protein C, protein S, and inhibition of factor V by activated protein C were normal.

Reinstitution of coumadin resulted in stabilization of serum creatinine and normalization of platelet count (>150 $\times$ 10^9/L on three determinations). The patient died during a bout of epigastric pain. Autopsy was not done.

This report supports the following approach to the diagnosis of APS. First, a battery of tests rather than a single test should be performed whenever APS is clinically suspected. This may be due to the heterogeneity of antiphospholipid antibodies or the high interlaboratory variation in test results [1–3]. Second, because of their high sensitivity, a silica-based APTT and HexPPANT should be included into the battery [4,5].

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An "All-Oral" Combination Therapy in Chronic Lymphocytic Leukemia Including the Oral Idarubicin

To the Editor: Oral idarubicin (IDA) has been evaluated as a single agent and in combination in acute myeloid leukemia (AML), and a substantial antileukemic effect has been demonstrated [1,2]. In low-grade non-Hodgkin lymphomas (NHL) IDA is now being utilized along with chlorambucil (CLB) and dexamethasone (DEX) to assess efficacy and toxicity when used as primary treatment [3]. However, to the best of our knowledges, studies dealing with the use of oral IDA in chronic lymphocytic leukemia (CLL) are virtually absent [4].

We treated six CLL patients considered resistant to conventional chemotherapies (CLB ± PDN, four cases; vincristine, cyclophosphamide, prednisone ± doxorubicin, two cases) in advanced clinical stage (stage B, 4, stage C, 2), median age 64 years (range, 55–76 years) with a "fully oral" combination, including IDA 12 mg/m^2 on days 1, 3, and 5, CLB 20 mg (total dose) on days 1–3 and prednisone (PDN) 50 mg (total dose) on days 1–5. Cycles were repeated every 28 days.

Preliminary results on the toxicity and efficacy of this "all-oral" regimen administered on an outpatient basis, after informed consent was achieved, are presented here. In all instances, therapy was well tolerated. After a median number of four courses of treatment (range, 1–5), no cardiotoxicity was clinically noted. Alopecia was not a problem. Despite the absence of antiemetic prophylaxis, neither acute nor delayed emesis was observed. Infectious toxicity (WHO, 2) could be demonstrated in a single patient. According to the National Cancer Institute (NCI) [5] response criteria in CLL, two patients were considered in partial remission (PR), three patients who did not show any change of pretreatment clinicohematological features were evaluated to meet criteria of stable disease (SD), progressive disease